

Nicotinic Acid Esters

BY JEROME G. KAUFMAN¹

Esters of nicotinic acid can be obtained by direct esterification of reaction mixtures that result when nicotine, quinoline or β -picoline is oxidized in the liquid phase. This direct synthesis is of interest because of the importance of these esters as intermediates in the preparation of the widely used nicotinamide. In addition, the esters, since they are capable of hydrolytic conversion to nicotinic acid in the body, can be classified as biologically active pyridine derivatives. It has been demonstrated that ethyl nicotinate, when administered orally, exhibits anti-black-tongue activity.²

This Laboratory³ has shown that good yields of nicotinic acid are obtained when nicotine, quinoline or β -picoline is oxidized by concentrated sulfuric acid in the presence of mercuric sulfate or selenium. In order to isolate the nicotinic acid formed, the sulfuric acid, always used in excess, is neutralized, and the product is precipitated as copper nicotinate. The latter is then converted to nicotinic acid in the usual way. If nicotinic acid esters were desired, it was necessary to esterify by any of the known methods.^{4,5,6,7}

Experimental

Methyl Nicotinate.—A mixture of 650 cc. of 95% sulfuric acid, 75 g. of selenium and 129 g. (1 mole) of quinoline was heated together for one hour. The maximum tem-

perature attained was 300°. During this time 240 cc. of water was distilled over. To the cooled mass was added 300 cc. of methanol, after which the mixture was refluxed for six hours on the steam-bath. The reaction mixture was then poured onto three times its volume of cracked ice, made alkaline with ammonium hydroxide, and extracted with ether. The combined ether extracts were washed with water and dried over anhydrous potassium carbonate. After the ether was removed, the product was vacuum-distilled. It yielded 82.5 g. of methyl nicotinate (b. p. (3 mm.) 70–72°), which immediately crystallized to beautiful white crystals in the receiver (m. p. 38°). The yield was 60.2%.

Ethyl Nicotinate.—With essentially the same procedure as described for methyl nicotinate, 83 g. of ethyl nicotinate (b. p. (4 mm.) 72–74°) was obtained; this yield was 55%.

Propyl Nicotinate.—Substitution of *n*-propyl alcohol for the methanol and ethanol used in the preceding experiments resulted in the formation of 93.5 g. of *n*-propyl nicotinate (b. p. (1 mm.) 80–82°). This represented a yield of 56.7%.

Nicotine and β -picoline behaved in a similar manner and gave yields of the esters in direct proportion to their ease of oxidation to nicotinic acid.⁸

(1) Present address: Van Ameringen-Haebler, Inc., Elizabeth, N. J.

(2) Woolley, Strong, Madden and Elvehjem, *J. Biol. Chem.*, **124**, 715 (1938).

(3) Woodward, Badgett and Kaufman, *Ind. Eng. Chem.*, **36**, 544 (1944).

(4) Pollak, *Monatsh.*, **16**, 46 (1895).

(5) Engler, *Ber.*, **27**, 1787 (1894).

(6) Camps, *Arch. Pharm.*, **240**, 353 (1902).

(7) LaForge, *THIS JOURNAL*, **50**, 2477 (1928).